# HYPOPERFUSION SIGNATURE IN HEALTHY SUBJECTS IN RISK OF DEVELOPING ALZHEIMER'S DISEASE

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**Target audience:**
Physicians, psychologists, radiologists and MR researchers.

**Purpose:**
To find abnormal features in brain imaging, both structural and physiological, in order to obtain early biomarkers for probable Alzheimer's disease (AD) development.

**Introduction:**
In this work, we investigate new biomarkers other than volume loss of hippocampi, entorhinal cortex and amygdala in the research criteria of AD[1]. Anatomical 3D T1 weighted images have been widely used to assess the volume and thickness of cortical and subcortical structures. Here we include the analysis of perfusion images through the Arterial Spin Labeling (ASL) technique to evaluate additional physiological changes. ASL is a non-invasive MRI technique, which allows the quantification of regional cerebral blood flow (rCBF) without contrast agents by labeling a small bolus of blood at the level of the carotid arteries with a radiofrequency pulse. This technique has shown its validity in detecting changes in mild cognitive impairment (MCI) and AD patients[2]. Our data comes from the Vallecas Project which is a longitudinal study that evaluates normal ageing in a cohort of more than 600 healthy elder people (ages between 70y and 85y). The prevalence (13%) of AD in people older than 65 years[3] suggests that a certain number of those subjects will develop AD in the next years.

**Methods:**
632 subjects underwent an MR scan on a 3T Signa HDx MR scanner (GE Healthcare, Waukesha, WI) using an eight-channel phased array coil. The first sequence was a 3DT1w SPGR with a TR=10.024ms, TE=4.56ms, TI=600ms, NEX=1, acquisition matrix=288x288, full brain coverage, resolution=1x1x1mm, flip angle=12. The second sequence was a 3D pCASL pulse sequence with full brain coverage, matrix size= 128x128, resolution=1.875x1.875x4mm, flip angle = 155, transit time=2.025s, TR=4.733s and TE=9.812ms was used to generate the rCBF maps. All 3DT1w were processed with Freesurfer[4] in order to obtain the cortical and subcortical volumes for each subject. The left and right hippocampi volume (LHV, RHV) was normalised by the total gray matter volume. This normalise measure allowed us to divide the sample into three groups: Control group ([LHV, RHV]>(mean hippocampus (MH)+1std.)), mean group (MH-2std.<[LHV, RHV]<MH+1std.) and probable AD group (PAD) ([LHV, RHV]<(MH-2std.)). We performed subsequent analyses comparing an age and gender matched Control (25subjects) and PAD (25subjects) groups. The 50 selected 3DT1w images were processed with the standard SPM DARTEL pipeline[5] and analysed with a General Linear Model (GLM) by means of a two sample t-test. The rCBF maps of the Control and PAD groups were processed with the ASL Toolbox[6] to obtain smoothed (FWHM=4x4x4mm), Partial Volume Effect corrected[7] and MNI-normalised perfusion maps for each subject. Again, statistical maps, using a two sample t-test analysis within the GLM were obtained.

**Results:**
As expected Fig.1 shows the results of gray matter changes using VBM-DARTEL between Control and PAD groups ($p_{FWE}<0.05$), depicting LH and RH volume loss in the PAD group. No CSF changes or an increase in ventricle volume are found. Fig. 2 and Fig. 3 show hypoperfusion patterns respectively in the PAD group compared to the Control group ($p_{FWE\_Cluster=300}=0.05$). Areas of hypoperfusion include: Caudate, hippocampi, thalamus, parahippocampal gyrus, amygdala, brodmann area 34, cingulate gyrus, precuneus and insula.
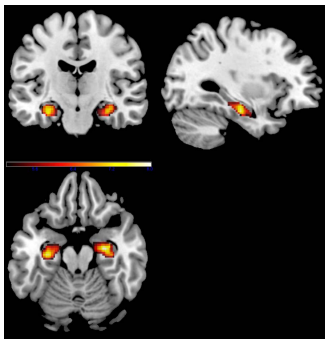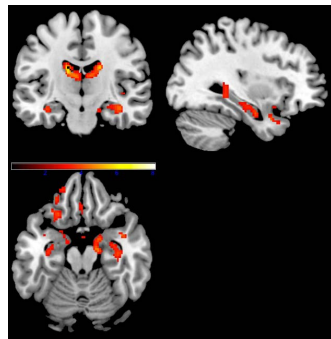


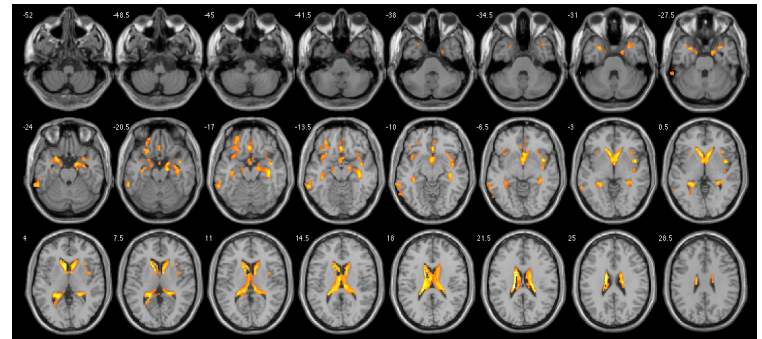Fig. 1 GM loss in PAD group    Fig. 2 Hypoperfusion in PAD group    Fig. 3 Pefusion loss in PAD group

**Discussion:**
A significant reduction in left and right hippocampi volume is found, supporting the idea that the PAD group is in risk of developing AD[1]. Several hypoperfusion patterns appear in those subjects in risk of developing AD. All regions where gray matter loss occur are included in regions with low perfusion. Besides, additonal regions of hypoperfusion are found suggesting that a loss in perfusion ocurrs prior to the neuron loss and gray matter atrophy[8]. Furthermore, ASL is proving to be more sensitive than gray matter volume analysis in key regions such as parahippocampal gyrus, amygdala and entorhinal cortex.

**Conclusion:**
We suggest the inclusion of perfusion studies to support the early diagnosis of AD and its presence in the standard research criteria for the diagnosis of AD.

**Acknowledgements:**

**References:**
[1] Dubois B., et al.; *Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria*; Lancet Neurol.; 2007; 6(8):734-746
[2] Johnson NA, et al.; *Pattern of Cerebral Hypoperfusion in Alzheimer Disease and Mild Cognitive Impairment Measured with Arterial Spin-labeling MR Imaging: Initial Experience;* Radiology; 2005; 234:851-859.
[3] *2012 Alzheimer's disease, facts and figures;* Alzheimer's Association; Alzheimer's & Dementia; 8(2)
[4] Freesurfer, http://surfer.nmr.mgh.harvard.edu; Accessed Nov. 11th 2013
[5] SPM, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/; Accessed Nov. 11th 2013
[6] ASL Toolbox, http://www.fundacioncien.es/areas/asl_toolbox.asp; Accessed Nov. 11th 2013
[7] Asllani I., et al.; *Regression Algorithm Correcting for Partial Volume Effects in Arterial Spin Labeling MRI*; MRM; 2009: 60:1362-1371
[8] Yvette I., et al.; *Resting state functional connectivity in preclinical Alzheimer's Disease*; Biol. Psychiatry; 2013; 74: 340-347